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Maternal concentrations of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) and duration of breastfeeding

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Maternal concentrations of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) and duration of breastfeeding. Fei C, McLaughlin JK, Lipworth L, Olsen J. *Scand J Work Environ Health*. 2010;36(5):413–421.

Objective Perfluorooctanoate (PFOA) has been associated with impaired lactation in mice. We examined whether maternal perfluorooctanesulfonate (PFOS) and PFOA concentrations correlated with duration of breastfeeding among women.

Methods We randomly selected 1400 pregnant women from the Danish national birth cohort (1996–2002) and measured PFOS and PFOA concentrations in early pregnancy by using high performance liquid chromatography/tandem mass spectrometry. Self-reported data on the duration of any and exclusive breastfeeding were collected twice during telephone interviews around 6 and 18 months after the birth of the child.

Results The duration of breastfeeding decreased with increasing concentrations of pregnancy PFOS and PFOA among multiparous women, for whom the adjusted odds ratios (OR) for weaning before 6 months of age were 1.20 (95% CI 1.06–1.37) per 10 ng/ml increase in PFOS concentrations and 1.23 (95% CI 1.13–1.33) per 1 ng/ml increase in PFOA concentrations. No consistent association was found for primiparous women.

Conclusions These findings suggest that PFOA and PFOS may reduce the ability to lactate, but could equally reflect reverse causation since no association was seen in primiparous women.

Key terms infant; maternal blood; perfluorinated chemicals; PFC.

Perfluorinated chemicals (PFC), including perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA), have been manufactured for more than 50 years. PFOS is used as stain and water repellent treatments for carpets, furniture, clothing, and food packaging, and as surfactants in cleaning products, shampoo, floor polishes, pesticide formulations, and fire-fighting foams (1). PFOA is primarily used as a surfactant and an emulsifier in the production of polytetrafluoroethylene (ie, Teflon) as well as fluoropolymers and fluoroelastomers. Both chemicals are widely present in humans, wildlife, and the environment. PFOS and PFOA exposure can result in a variety of toxic effects among animals, including liver toxicity, developmental toxicity, and immunotoxicity (2). Adverse effects on reproductive organs have also been reported (3, 4).

Recently, several studies have shown that short term exposure to PFOA may delay mammary gland

development among mice. Treatment with 5 mg PFOA/kg during pregnancy caused a significant reduction in mammary differentiation, as well as delays in epithelial involution and alterations in milk protein gene expression among mice, suggesting that PFC may interfere with the ability to lactate (4). The potential effect on mammary gland development is apparent when the exposure occurs during the lactation or peripubertal period (5, 6). Additionally, a decrease in weight gain was observed in rodent neonates if their mothers were exposed to high dosage of PFOA and PFOS (7, 8), which indirectly suggests that poor quantity or quality of milk may be a possible pathway to postnatal growth retardation. Mammary glands are sensitive to PFOA exposure in rodent models, and serum PFOA concentrations of around 2000 ng/ml have been sufficient to produce abnormal development and differentiation (6).

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The effective concentrations in experimental animals have been of similar magnitude to concentrations in occupationally exposed workers, or 4–5 times higher than has been reported for individuals living in highly exposed communities (9, 10). These concentrations are still substantially higher than the concentrations found among the general population (average PFOA concentration in the US population is 4–5 ng/ml) (11). Moreover, PFOA or PFOS may have estrogenic effects, although the evidence from in vivo or in vitro studies is inconsistent (12–17), and their potential effects on hormones, including prolactin, oxytocin, and estrogen may influence lactation. It is thus important to study if these compounds affect lactation at the concentrations found in humans.

The health benefits of breastfeeding are well documented, including decreased infant mortality and morbidity and lower risk of breast and ovarian cancers for the mother (18). Despite these benefits, breastfeeding duration rates remain low in many countries (19, 20). However, Danish women have a strong tradition of breastfeeding and have long maternity leave. In this paper, we used data from the Danish national birth cohort to investigate if PFOA and PFOS concentrations in maternal blood correlate with decreased duration of breastfeeding.

Methods

Subjects

The women were enrolled into the Danish national birth cohort, a nationwide follow-up study of almost 100 000 children and their mothers (21). Briefly, pregnant women were recruited through their general practitioners around weeks 6–12 of gestation (30% of eligible women in Denmark and about 60% of those invited by their general practitioners participated in this cohort study). Self-reported data were collected twice by computer-assisted telephone interviews during pregnancy and twice after birth. Two maternal blood samples taken during pregnancy and one umbilical cord blood sample obtained shortly after birth were stored in the cohort's biobank.

Our study was designed primarily to estimate the potential effects of PFOA and PFOS on fetal growth and postnatal development of the child (22, 23). We randomly sampled 1400 women and their children among those 43 045 who fulfilled the following selection criteria: (i) provided the first maternal blood sample, (ii) gave birth to a single live born child without congenital malformation (prevalence of multiple birth or congenital malformation is 4% in the Danish cohort), and (iii) completed all four telephone interviews.

Written informed consent was obtained from all participants upon recruitment. The University of California Los Angeles (UCLA) Office for Protection of Research Subjects (Reference No 06–08–023–01) and the Danish Data Protection Agency (Reference No J Nr 2006–41–6324) approved the study protocol.

PFOA and PFOS exposure

We used maternal blood samples taken at the first antenatal visit (weeks 4–14 of pregnancy) for this study. Concentrations of PFOS and PFOA in plasma were measured by high performance liquid chromatography/tandem mass spectrometry at the 3M Toxicology Laboratory (24). Stable-labeled analogs of PFOS ($^{18}\text{O}_2$ PFOS) and PFOA ($^{13}\text{C}_2$ PFOA) were used during extractions, which were performed using solid phase extraction techniques and based on 100 μl of plasma. All values were above the lower limit of quantitation (LLOQ) of 1 ng/ml, except one PFOA value that was assigned a value of half the LLOQ (ie, 0.5 ng/ml). Further details about the analysis methods were given in our earlier report (22). The laboratory was blinded to any information about the pregnant women.

Duration of Breastfeeding

Data on infant feeding practices were collected in the interviews at 6 and 18 months after birth (see information on the Danish national birth cohort for details: www.dnbc.dk). In this study, “exclusive” breastfeeding was defined as breastfeeding without giving the infant anything else except water and vitamins, a modification of the World Health Organization (WHO) definition [ie, no supplemental liquids or solid foods other than human milk and medications or vitamins (25)]. At the 6-month interview, mothers reported the duration of exclusive breastfeeding in months, weeks, and days. The women were also asked about the infant's age at first and regular use of formula milk (including in the form of powder gruel or dietary supplement mixtures) or cow's milk. Introduction of any food item other than human milk terminates exclusive breastfeeding, and for that reason we compared the reported duration of exclusive breastfeeding with the ages at which formula milk or cow's milk was first or regularly used. If these values differed by >2 weeks and the reported value for the duration of exclusive breastfeeding was greater than the ages at which those foods were introduced ($N=50$), the duration of exclusive breastfeeding was set to the infant's age at the use of formula milk or cow's milk, whichever was earlier (26). Otherwise, the reported value for the duration of exclusive breastfeeding was used. Thus, the definition of exclusive breastfeeding in this study came as close as possible to the WHO definition.

We twice asked the mothers when they stopped breastfeeding (ie, weaning age), once in the 6-month interview and once in the 18-month interview. For those mothers who provided inconsistent responses (N=25), we chose the younger of the two possible ages. One hundred and sixty-two mothers did not answer the questions related to weaning age in both interviews, but they did report in the 6-month interview if the child was still being breastfed at that time, or in the 18-month interview if the child was still breastfed after it turned 6 months old. Of these 162 women, 53 gave inconsistent responses; duration of breastfeeding before weaning was therefore set as a missing value in these cases. For the others, duration was censored at the date of the 6-month interview or the date on which the child turned 6 months of age, whichever came first.

Statistical analysis

Cox proportional hazard analysis was performed to estimate the hazard ratio (HR) of earlier weaning or termination of exclusive breastfeeding over time since birth. We also categorized whether each child was breastfed for 3 or 6 months, and exclusively breastfed for 1 or 4 months. The cut-off points were chosen at 6 months for any breastfeeding and 4 months for exclusive breastfeeding because the Danish government recommends that complementary foods should be introduced between 4 and 6 months. Only few mothers continued exclusive breastfeeding beyond 6 months in our dataset (N=60). To examine if women with higher PFOA and PFOS exposure concentrations were at a risk of earlier termination of breastfeeding, the durations of breastfeeding were further dichotomized at the cut-off points of 3 months for any breastfeeding and 1 month for exclusive breastfeeding. Logistic regression was used to examine the association between PFC concentrations and the above-mentioned categorical outcomes. We also performed the analyses stratified by parity. PFOS and PFOA concentrations were categorized a priori into quartiles using the lowest quartile as the reference group (6.4–26.0, 26.1–33.3, 33.4–43.2, ≥ 43.3 ng/ml for PFOS and the LLOQ (1 ng/ml)–3.90, 3.91–5.20, 5.21–6.96, ≥ 6.97 ng/ml for PFOA).

Variables considered potential confounders were: (i) maternal age at time of delivery (<25, 25–29, 30–34, ≥ 35 years), (ii) parity (continuous), (iii) pre-pregnancy body mass index (BMI) (underweight <18.5 kg/m², normal weight 18.5–24.9 kg/m², overweight 25.0–29.9 kg/m², obese ≥ 30.0 kg/m²), (iv) maternal socioeconomic status (high, middle, low), (v) alcohol consumption (0, <1, 1–<2, ≥ 2 drinks/week), (vi) smoking (non-smoker, stopped smoking during pregnancy, 1–9 cigarettes/day, ≥ 10 cigarettes/day during pregnancy), and (viii) gestational age at time of blood drawing (weeks). We defined maternal

socioeconomic status according to women's education and current job titles. Women with a higher education (four years beyond secondary school education) or in management level jobs were classified as "high" social status; women with middle-range training and skilled workers were classified as "middle"; and unskilled workers or the unemployed were classified as "low." We also evaluated other possible determinants of breastfeeding, such as paternal education and occupation (as an indicator of family support for breastfeeding), physical exercise during the last trimester of pregnancy, and the infant's gender, but they did not change the estimates.

A sensitivity analysis was done for primiparous women. We hypothesized that maternal PFOA and PFOS concentrations in plasma during the second pregnancy were reduced by excretion into breast milk. We used data on PFOA and PFOS concentrations in breast milk estimated by Tao et al (27), which were 0.131 ng/ml for PFOS and 0.0438 ng/ml for PFOA. Suppose that that average daily milk productions are 800 ml during the first 0–6 months after delivery, 500 ml during 6–9 months, and 400 ml after 9 months. The average human blood volume is 4700 ml. As a result, plasma PFC concentrations during their second pregnancy are:

$$C \text{ (ng/ml)} = C_1 - \sum_i^n \frac{C_i \times V_i \times D_i}{4700}$$

Where C_1 = maternal PFC concentrations in plasma measured in the first pregnancy (ng/ml); C_i = PFC concentrations in breast milk for the first baby (ng/ml); V_i = average daily breast milk productions for the first baby (ml); D_i = duration of breastfeeding (days) for the first child.

We have no prior data on PFC uptake between birth intervals, and could not take this into consideration. If the simulated values were negative or <1 ng/ml, they were assigned a value of 0.5 ng/ml (half the LLOQ). Data on the duration of breastfeeding of the first child were arbitrarily used for the simulated breastfeeding of the second child.

Results

Demographic and maternal characteristics of the study population have been described elsewhere (22). The average age at time of delivery was about 30 years, and about half of the women were expecting their first child. One-third were overweight or obese, based on BMI before pregnancy. Plasma concentrations of PFOA and PFOS concentrations measured early in pregnancy were similar to most concentrations reported for the general population during a comparable time period (11, 28). PFOS and PFOA concentrations decreased with

increasing parity, and were 9% and 29% lower among multiparous than primiparous women, respectively, after adjustment for maternal age. Higher PFC concentrations were also observed among overweight and obese women (mean=37.1 ng/ml for PFOS and 5.7 ng/ml for PFOA), compared with women of a normal weight (mean = 34.5 ng/ml for PFOS and 5.5 ng/ml for PFOA) (15).

The median duration of any breastfeeding (N=1238, excluding 109 censored data and 53 missing data) was 34.3 weeks [interquartile range (IQR) 17.1–42.8]. Approximately 15% (205 out of 1347) discontinued breastfeeding before the child turned 3 months of age. Sixty-five percent (871 out of 1347) still breastfed the child at 6 months of

age while 16% (204 out of 1238) continued to breast-feed the child at age 12 months. The median duration of exclusive breastfeeding was 17.1 weeks (IQR 12.8–21.4). Twenty-two women never breastfed their infants; at the end of the first week postpartum, 16 women stopped any breastfeeding and 43 women stopped exclusive breastfeeding. One thousand and twenty two (1022) women provided data on exclusive breastfeeding, and two-thirds of their infants were still exclusively breastfed at 4 months of age but only 6% at 6 months.

Higher maternal PFOS and PFOA concentrations were associated with shorter duration of breastfeeding (table 1). Women who breastfed the child longer

Table 1. Characteristics of the women and infants included in the study, by duration of any breastfeeding. [IQR=interquartile range; SD=standard deviation; PFOS = perfluorooctanesulfonate; PFOA= perfluorooctanoate; BMI=body mass index; SES=socioeconomic status]

Characteristic ^a	N	<3 months (N=205)		3–<6 months (N=271)		≥6 months (N=871)	
		Medium (IQR) or mean (SD)	%	Medium (IQR) or mean (SD)	%	Medium (IQR) or mean (SD)	%
PFOS (ng/ml)	1346	37.0 (28.0–46.9)	..	35.1 (28–45.6)	..	32.3 (24.6–41.4)	..
PFOA (ng/ml)	1346	5.90 (4.65–7.45)	..	5.65 (4.26–7.26)	..	4.96 (3.57–6.68)	..
Maternal age at delivery (year)	1313	29.3 (4.7)	..	29.9 (4.5)	..	31.2 (4.2)	..
Pre-pregnancy BMI (kg/m ²)	1314	25.1 (4.8)	..	24.3 (4.3)	..	23.3 (3.8)	..
Birthweight (g)	1347	3546.2 (512.5)	..	3607.1 (553.4)	..	3657.8 (516.9)	..
Gestational age (weeks)	1336	39.9 (1.6)	..	40.0 (1.7)	..	40.1 (1.5)	..
Duration of exclusive breast-feeding (weeks) ^b	982	3.6 (3.2)	..	13.2 (5.7)	..	19.0 (4.6)	..
Parity							
0	601	..	15.8	..	22.8	..	61.4
1	486	..	15.8	..	18.3	..	65.8
≥2	260	..	12.7	..	17.3	..	70.0
Maternal SES							
Higher	681	..	11.2	..	17.0	..	71.8
Middle	545	..	17.3	..	23.9	..	58.9
Lower	117	..	29.1	..	20.5	..	50.4
Smoking during pregnancy							
Non-smoker	1010	..	12.4	..	18.6	..	69.0
Stopped smoking	127	..	13.4	..	22.1	..	64.6
1–9 cigarettes/day	103	..	24.3	..	25.2	..	50.5
≥10 cigarettes/day	107	..	35.5	..	27.1	..	37.4
Alcohol consumption during the pregnancy							
Non-drinker	746	..	17.2	..	20.0	..	62.9
<1 drink/week	208	..	14.9	..	16.8	..	68.3
1–<2 drinks/week	218	..	11.5	..	19.3	..	69.3
≥2 drinks/week	159	..	11.3	..	26.4	..	62.3
Infant gender							
Girl	667	..	14.7	..	19.0	..	66.3
Boy	680	..	15.7	..	21.2	..	63.1
Cesarean delivery							
No	1146	..	13.9	..	19.8	..	66.3
Yes	200	..	23.0	..	22.0	..	55.0

^a Missing data: PFOA and PFOS concentrations (N=1), maternal age (N=1), pre-pregnancy BMI (N=33), maternal SES (N=4), alcohol consumption during the pregnancy (N=16); birthweight (N=11), gestational age (N=1), cesarean delivery (N=1)

^b The number of women who provided data on exclusive breastfeeding were 147, 199, 636, respectively.

were *less likely* to be first-time mothers, be obese, have smoked during pregnancy, or have had a cesarean delivery. They were *more likely* to be of higher socioeconomic status and have a baby with a larger birth weight.

For women who were having their first child, a statistically significant positive association was observed only between PFOS and weaning before 6 months [odds ratio (OR) 1.20 per 10 ng/ml increase in PFOS concentrations 95% confidence interval (95% CI) 1.04–1.37 (table 2)]. Among the 746 multiparous women, the proportion of women who stopped breastfeeding

before the child reached 3 or 6 months of age increased with increasing PFC concentrations; specifically, we observed a 20% (OR 1.20, 95% CI 1.06–1.37) increase in the risk of weaning before 6 months of age per 10 ng/ml increase in PFOS concentrations, and a 23% (OR 1.23, 95% CI 1.13–1.33) increase per 1 ng/ml increase in PFOA concentrations. The magnitude of risk increase in terminating breastfeeding before the child reached 3 months of age was similar to that for 6 months of age. The Cox models using duration of breastfeeding in weeks also showed that higher PFC concentrations

Table 2. Adjusted odds ratios (OR) for weaning before 3 and 6 months and hazard ratios (HR) for duration of any breastfeeding (weeks), by maternal perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations (ng/ml) in quartiles. [95% CI= 95% confidence intervals; LLOQ=lower limit of quantitation.]

Exposure	N	Weaning before 3 months			Weaning before 6 months			HR	95% CI ^a
		%	OR	95% CI	%	OR	95%CI		
All (N=1346) ^b									
PFOS (ng/ml)									
6.4–26.0	339	11.2	1.00 reference		25.7	1.00 reference		1.00 reference	
26.1–33.3	332	14.2	1.26	0.78–2.03	35.5	1.56	1.10–2.22	1.23	1.05–1.44
33.4–43.2	334	15.6	1.26	0.78–2.04	37.4	1.54	1.08–2.19	1.23	1.04–1.46
≥43.3	341	19.9	1.89	1.19–3.01	42.8	2.07	1.46–2.93	1.40	1.18–1.65
Per 10 ng/ml	..	..	1.17	1.04–1.32	..	1.19	1.09–1.31	P for trend <0.01	
PFOA (ng/ml)									
<LLOQ–3.90	334	9.0	1.00 reference		23.0	1.00 reference		1.00 reference	
3.91–5.20	332	15.4	1.95	1.17–3.24	34.9	1.88	1.31–2.72	1.21	1.03–1.43
5.21–6.96	337	16.3	2.02	1.21–3.38	39.8	2.22	1.54–3.22	1.34	1.13–1.59
≥6.97	343	20.1	2.68	1.60–4.50	43.4	2.60	1.78–3.81	1.40	1.17–1.68
Per 1 ng/ml	..	..	1.09	1.02–1.15	..	1.10	1.05–1.16	P for trend<0.01	
Primiparous (n=600) ^c									
PFOS (ng/ml)									
6.4–26.0	106	15.1	1.00 reference		34.0	1.00 reference		1.00 reference	
26.1–33.3	134	13.4	0.95	0.44–2.04	34.3	1.06	0.60–1.89	0.96	0.73–1.26
33.4–43.2	172	13.4	0.70	0.34–1.46	37.2	1.01	0.59–1.74	0.99	0.76–1.29
≥43.3	188	20.2	1.24	0.62–2.46	45.7	1.52	0.89–2.60	1.17	0.90–1.52
Per 10 ng/ml	..	..	1.12	0.94–1.34	..	1.20	1.04–1.37	P for trend=0.17	
PFOA (ng/ml)									
<LLOQ–3.90	45	11.1	1.00 reference		33.3	1.00 reference		1.00 reference	
3.91–5.20	131	18.3	1.95	0.67–5.66	34.4	1.04	0.48–2.22	0.90	0.62–1.30
5.21–6.96	177	12.4	1.16	0.40–3.38	38.4	1.28	0.61–2.68	0.90	0.63–1.30
≥6.97	247	17.8	1.82	0.66–5.07	42.1	1.50	0.74–3.06	0.98	0.69–1.38
Per 1 ng/ml	..	..	1.02	0.93–1.10	..	1.03	0.97–1.10	P for trend=0.67	
Multiparous (N=746) ^b									
PFOS (ng/ml)=									
6.4–26.0	233	21.9	1.00 reference		9.4	1.00 reference		1.00 reference	
26.1–33.3	198	36.4	2.05	1.30–3.23	14.6	1.55	0.82–2.91	1.42	1.16–1.73
33.4–43.2	162	37.6	2.11	1.31–3.40	17.9	1.99	1.04–3.78	1.45	1.17–1.80
≥43.3	153	39.2	2.55	1.57–4.13	19.6	2.64	1.38–5.02	1.55	1.24–1.94
Per 10 ng/ml	..	..	1.25	1.06–1.48	..	1.20	1.06–1.37	P for trend<0.01	
PFOA (ng/ml)									
<LLOQ–3.90	289	21.4	1.00 reference		8.6	1.00 reference		1.00 reference	
3.91–5.20	201	35.3	2.24	1.46–3.45	13.4	1.82	0.98–3.38	1.24	1.02–1.50
5.21–6.96	160	41.3	2.68	1.69–4.23	20.6	2.92	1.58–5.40	1.48	1.20–1.82
≥6.97	96	46.9	3.55	2.08–6.06	26.0	3.97	2.01–7.86	1.64	1.27–2.10
Per 1 ng/ml	..	..	1.24	1.12–1.36	..	1.23	1.13–1.33	P for trend<0.01	

^a The P-values for trend tests of HR were given for the four-quartile comparison of PFOA and PFOS concentrations.

^b The estimates were adjusted for maternal age at delivery, parity, pre-pregnancy body mass index (BMI), maternal socioeconomic status, alcohol consumption, and smoking during pregnancy and gestational age at blood drawing.

^c The estimates were adjusted for maternal age at delivery, pre-pregnancy body mass index (BMI), maternal socioeconomic status, alcohol consumption, and smoking during pregnancy, and gestational age at blood drawing.

were significantly associated with shorter duration of any breastfeeding among multiparous but not primiparous women. Similar results were observed for exclusive breastfeeding (table 3).

The sensitivity analysis showed that the association estimates for the simulated second breastfeeding were shifted upward, compared with the original results from primiparous women (see appendix). However, when compared with the original results from multiparous women, the strength of the associations was similar for PFOS and slightly weaker for PFOA.

Discussion

Our results suggest that higher maternal concentrations of PFOA and PFOS may be associated with a shorter duration of both any and exclusive breastfeeding among multiparous women. Among primiparous women, no consistent association was observed.

The associations observed among multiparous women may reflect a non-causal association, similar to what has been suggested for

Table 3. Adjusted odds ratios (OR) for termination of exclusive breastfeeding before 1 and 4 months and hazard ratios (HR) for duration of exclusive breastfeeding (weeks), by maternal perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations (ng/ml) in quartiles. [95% CI= 95% confidence intervals; LLOQ=lower limit of quantitation]

Exposure	N	Termination of exclusive breastfeeding before 1 month			Termination of exclusive breastfeeding before 4 months			HR	95% CI ^a
		%	OR	95% CI	%	OR	95%CI		
All (N=1021) ^b									
PFOS (ng/ml)									
6.4–26.0	274	9.8	1.00 reference		26.3	1.00 reference		1.00 reference	
26.1–33.3	269	12.3	1.25	0.72–2.18	35.5	1.54	1.04–2.27	1.24	1.04–1.47
33.4–43.2	245	9.0	0.84	0.45–1.54	31.4	1.25	0.83–1.88	1.14	0.96–1.37
≥43.3	233	15.9	1.55	0.89–2.71	40.8	1.86	1.24–2.79	1.37	1.14–1.64
Per 10 ng/ml	..	..	1.09	0.93–1.27	..	1.14	1.02–1.27	P for trend <0.01	
PFOA (ng/ml)									
<LLOQ–3.90	286	7.3	1.00 reference		21.7	1.00 reference		1.00 reference	
3.91–5.20	277	13.4	1.90	1.04–3.40	36.8	2.14	1.43–3.20	1.16	0.98–1.38
5.21–6.96	241	11.2	1.60	0.82–2.93	34.8	1.96	1.28–3.01	1.22	1.01–1.47
≥6.97	217	15.7	2.19	1.16–4.14	41.9	2.59	1.66–4.04	1.37	1.12–1.69
Per 1 ng/ml	..	..	1.05	0.98–1.13	..	1.06	1.00–1.12	P for trend<0.01	
Primiparous (N=462) ^c									
PFOS (ng/ml)									
6.4–26.0	86	16.3	1.00 reference		38.4	1.00 reference		1.00 reference	
26.1–33.3	114	12.3	0.71	0.31–1.63	38.6	1.12	0.61–2.07	1.14	0.85–1.52
33.4–43.2	129	5.4	0.27	0.10–0.73	30.2	0.70	0.38–1.29	1.05	0.79–1.39
≥43.3	133	15.8	0.78	0.35–1.70	43.6	1.19	0.66–2.15	1.23	0.93–1.64
Per 10 ng/ml	..	..	0.98	0.78–1.23	..	1.04	0.89–1.22	P for trend=0.21	
PFOA (ng/ml)									
<LLOQ–3.90	40	20.0	1.00 reference		42.5	1.00 reference		1.00 reference	
3.91–5.20	121	15.7	0.74	0.28–1.94	39.7	0.81	0.38–1.75	1.08	0.75–1.56
5.21–6.96	135	5.9	0.26	0.09–0.78	31.1	0.59	0.28–1.28	0.96	0.67–1.38
≥6.97	166	12.6	0.55	0.21–1.42	40.4	0.91	0.43–1.89	1.16	0.81–1.66
Per 1 ng/ml	..	..	0.93	0.82–1.06	..	0.98	0.91–1.06	P for trend=0.43	
Multiparous (N=559) ^b									
PFOS (ng/ml)									
6.4–26.0	188	6.9	1.00 reference		20.7	1.00 reference		1.00 reference	
26.1–33.3	155	12.3	2.14	0.98–4.71	32.9	1.88	1.10–3.19	1.31	1.05–1.63
33.4–43.2	116	12.9	2.27	0.99–5.21	32.8	2.01	1.14–3.56	1.17	0.92–1.48
≥43.3	100	16.0	3.17	1.38–7.30	37.0	2.80	1.56–5.04	1.47	1.14–1.89
Per 10 ng/ml	..	..	1.26	1.01–1.58	..	1.28	1.09–1.51	P for trend<0.01	
PFOA (ng/ml)									
<LLOQ–3.90	246	5.3	1.00 reference		18.3	1.00 reference		1.00 reference	
3.91–5.20	156	11.5	2.76	1.26–6.05	34.6	2.71	1.64–4.48	1.16	0.94–1.42
5.21–6.96	106	17.9	4.39	1.94–9.95	39.6	3.56	2.02–6.25	1.40	1.10–1.77
≥6.97	51	25.5	7.96	3.11–20.38	47.1	4.77	2.35–9.70	1.49	1.09–2.04
Per 1 ng/ml	..	..	1.30	1.14–1.49	..	1.27	1.14–1.42	P for trend<0.01	

^a The P-values for trend tests of HR were given for the four-quartile comparison of PFOA and PFOS concentrations.

^b The estimates were adjusted for maternal age at delivery, parity, pre-pregnancy body mass index (BMI), maternal socioeconomic status, alcohol consumption and smoking during pregnancy and gestational age at blood drawing.

^c The estimates were adjusted for maternal age at delivery, pre-pregnancy BMI, maternal socioeconomic status, alcohol consumption and smoking during pregnancy, and gestational age at blood drawing.

dichlorodiphenyldichloroethylene (DDE) (29, 30). Women who previously breastfed longer are more likely to do so again (31, 32), and longer lactation would reduce concentrations of PFOS and PFOA by excreting them into breast milk (27, 33–35). Thus, the association we observed between the duration of breastfeeding and PFC among multiparous women may therefore reflect previous breastfeeding experiences and explain the lower concentrations of PFC among women who breastfed for a longer time, as indicated by our simple sensitivity analysis. However, this analysis was limited by a lack of prior data on uptake between birth interval and excretion by other pathways. On the other hand, parity does not accurately capture previous breastfeeding experience, and this explanation remains speculative. The association we observed may also have a causal interpretation. Hormonal concentrations differ between multiparous and primiparous women. It has been shown that serum levels of prolactin were lower among multi- than primiparas (36). They also have different lactation performance, such as early suckling, numbers of feedings, milk intake in neonates and use of formula (37). As a result, these related factors may modify the association between PFC and breastfeeding.

Although we asked the questions on breastfeeding practice while the women were still breastfeeding and the potential for recall bias is therefore minimal, other biases may have arisen from inaccuracies in measurement of breastfeeding duration. Detailed information about other aspects of infant feeding practice, including introduction of formula, cow's milk, and complementary food, were collected and so the duration of exclusive and any breastfeeding could be determined. As expected, primiparity, obesity, lower socioeconomic status, smoking during pregnancy, and cesarean delivery were associated with early weaning, a finding that was consistent with other publications (26, 38).

We do not have empirical data on whether breastfeeding duration was determined by factors such as inability to produce sufficient milk or infant's failure to thrive, or by external factors, such as social conditions, health problems, pregnancy, or other factors. However, almost all women in Denmark receive paid maternity leave for at least six months postpartum, and they receive strong support from midwives, lactation consultants, and other health providers after delivery. Breastfeeding practice is almost universal and rarely terminated during the first six months if it occurs without problems (31, 39); thus, the influence of certain social variables on breastfeeding practices is likely to be minimal. Furthermore, it is unlikely that cosmetic or other non-medical reasons for terminating breastfeeding correlated with plasma PFC concentrations. In addition, adjustment for socioeconomic variables is likely to reduce any residual confounding related to the

association between duration of breastfeeding and the time at which women return to work following delivery.

The Danish national birth cohort used a number of different questions to describe infant feeding practices. We took a conservative approach in determining the duration of exclusive breastfeeding, and there was no significant difference in PFOA or PFOS concentrations between women with and without consistent responses for the duration of exclusive breastfeeding. A sub-analysis using original values of exclusive breastfeeding (the values were not corrected when they were not consistent with the infant's age at the use of formula or cow's milk) showed that the estimates were very robust.

In conclusion, our data suggest that exposure to PFOA and PFOS at concentrations found in the general population may be associated with shorter duration of breastfeeding. Since the association was restricted to multiparous women, a spurious association reverse causation is a plausible alternative explanation since duration of breastfeeding correlates between pregnancies and PFC are excreted in breast milk, albeit in low concentration.

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Appendix. Adjusted odds ratios (OR) for weaning before 3 and 6 months and hazard ratios (HR) for duration of any breastfeeding (weeks), by maternal perfluorinated chemical (PFC) levels (ng/ml) in quartiles (N=600) – a sensitivity analysis. [95% CI= 95% confidence interval; LLOQ=lower limit of quantification]

Exposure	N	Weaning before 3 months			Weaning before 6 months			HR	95% CI ^a
		%	OR	95% CI ^b	%	OR	95% CI ^b		
PFOS (ng/ml)									
<26.0	193	11.9	1.00	reference	27.5	1.00	reference	1.00	reference
26.1–33.3	145	12.9	0.87	0.44–1.71	38.8	1.49	0.92–2.42	1.19	0.95–1.50
33.4–43.2	143	18.2	1.29	0.67–2.47	40.6	1.56	0.95–2.56	1.35	1.07–1.70
≥43.3	118	23.1	1.81	0.94–3.48	54.7	2.79	1.67–4.68	1.62	1.26–2.09
Per 10 ng/ml	..	..	1.19	0.94–3.48	..	1.32	1.15–1.52	P for trend<0.01	
PFOA (ng/ml) ^c									
<LLOQ–3.90	218	13.3	1.00	reference	28.0	1.00	reference	1.00	reference
3.91–5.20	129	13.2	0.96	0.49–1.88	41.9	1.98	1.21–3.24	1.17	0.92–1.47
5.21–6.96	145	18.6	1.53	0.84–2.79	44.1	2.17	1.35–3.47	1.30	1.04–1.62
≥6.97	108	20.4	1.65	0.87–3.15	49.1	2.70	1.61–4.52	1.50	1.16–1.92
Per 1 ng/ml	..	..	1.06	0.98–1.14	..	1.13	1.04–1.21	P for trend<0.01	

^a The P-values for trend tests of HR were given for the four-quartile comparison of PFOS levels.

^b The estimates were adjusted for maternal age at delivery, pre-pregnancy body mass index (BMI), maternal socioeconomic status, alcohol consumption and smoking during pregnancy, and gestational age at blood drawing.

^c The values of PFOA concentrations lower than 1 ng/ml (n=135) were assigned a value of 0.5 ng/ml.